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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/602,373 | 06/23/00 | ZHU | L 25636-702 |

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| EXAMINER | |
|---|---|
| PRASTHOFER, T | |
| **ART UNIT** | **PAPER NUMBER** |
| 1627 | 11 |

**DATE MAILED:** 09/25/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/602,373 | Applicant(s) ZHU ET AL. | |
|---|---|---|---|
| | Examiner Thomas W Prasthofer | Art Unit 1627 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 June 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-15,19,23,24 and 25-50* is/are pending in the application.

4a) Of the above claim(s) *25-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-15,19,23,24 and 44-50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

# Detailed Action

## Status of the Application

Receipt is acknowledged of a response to an office action with amendment on June 27, 2001 in Paper No. 10.

## Status of the Claims

Claims 1-43 were pending in the present application. Claims 25-43 were withdrawn from further consideration by the examiner in Paper No. 9. Applicant cancelled claims 16-18 and 20-22 and added new claims 44-50 in Paper No. 10. Claims 1-15, 19, and 23-50 are pending in the present application. Claims 1-15, 19, 23, 24, and 44-50 are being examined on their merits.

## Withdrawn Objections/Rejections

1. The objection to claim 8 is withdrawn in response to applicant's amendment.

2. The rejections of claims 1-24 under 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph in the office action mailed March 20, 2001 (Paper No. 9) are withdrawn in response to applicant's arguments.

3. The rejections of claims 2-4 under 35 U.S.C. 112, second paragraph over the term "about" in Paper No. 9 are withdrawn in response to applicant's amendments and arguments.

4. The rejections of claims 16-18, 21, and, 22 under 35 U.S.C. 112, second paragraph in paragraphs 11-17 of Paper No. 9 are withdrawn in response to applicant's cancellation of claims 16-18 and 20-22 in Paper No. 10.

5. The rejection of claims 1-24 under 35 U.S.C. 103(a) over Filupa et al., Hua et al., and Hoeffler et al. is withdrawn to simplify prosecution of the application. The examiner considers the rejection to be substantially a duplicate of the rejection under 35 U.S.C. 103(a) over the same three references in a different order (Hoeffler et al., Hua et al. and Filupa et al.). By withdrawing this rejection, examiner does not in any way imply that the rejection is not completely correct. The examiner merely wishes to remove an unnecessary duplication.

## Maintained Rejections

The statutory basis for any rejections not provided below can be found in an earlier office action.

## Maintained Rejections – 35 U.S.C. 103

6. Claims 1-15, 19, 23, 24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeffler et al. (1999) WO 99/28502, Hua et al (1997) Plasmid 38:91-96, and Filupa et al. (1998) WO 98/49198 for reasons made of record in Paper No. 9.

Applicant argues that Hoeffler et al. teach single chain antibody library construction *in vitro* while the present invention constructs single chain antibody libraries *in vivo*, and that the library diversity of Hoeffler et al. is only $3.6x10^6$ while the library diversity of the presently claimed invention is at least $1x10^7$. Applicant argues that the Hoeffler et al. reference teaches away from the claimed invention because the reference teaches that library diversity need not be much greater than $10^6$ "since the transformation capacity of yeast is generally $10^7$ or below."

Applicant argues that the Hua et al. reference teaches only a method of optimizing homologous recombination in yeast and that the Hua et al. reference fails to teach shortcomings in the method of Hoeffler et al. or the production of libraries of single chain antibodies.

Applicant argues that the Filupa et al. reference teaches the synthesis of single chain antibodies in capable of glycosylation and that the reference does not teach or suggest how to modify Hoeffler et al.

Applicant's arguments have been carefully considered and are found not to be persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, motivation is provided in the references that would suggest to one of ordinary skill in the art to combine the cited methodologies.

The Hoeffler et al. reference teaches that there is a need in the art for "*a method of screening for and isolating single-chain fragments of immunoglobulins variable domains capable of targeting characteristic transcription factors and related biomelecules in vivo*" (page 4). The Hoeffler et al. reference also teaches a method for constructing libraries of single-chain fragments of variable domains (scFvs) in host cells including bacteria and yeast (abstract and claim 9, for example). The use of transcription factor fusion proteins to detect binding during screening is also taught (claim 9, for example). The Hoeffler et al. reference does not teach away from libraries of diversity greater than $10^7$. The reference merely states a limitation of the method that is imposed by transformation efficiency and in no way implies that libraries of greater diversity are not desired.

The Hua et al. reference teaches an homologous recombination method for cloning in yeast. The reference teaches that:

"*Functional analysis of a new gene usually involves many molecular biological technologies, including...yeast two hybrid systems for studying protein-protein interactions. These technologies involve many steps of DNA manipulation and are rather time-consuming. Simplifying the cloning process would increase research efficiency and reduce the cost of investigation.*" (page 91, column 1)

Here the Hua et al. reference provides motivation for one of ordinary skill in the art to apply the method of homologous recombination to large scale screenings of protein-protein interactions (such as antibody-antigen or scFv-antigen interactions). The limitation with respect to transformation efficiency cited in the Hoeffler et al. reference does not apply to the Hua et al. method. One would have had reasonable expectation for success because no new methods or reagents would be required and the methods employed had all been demonstrated to be operable.

The Filupa et al. reference teaches preferred linkers to be used in scFvs.

With respect to library diversity, it would have been obvious to one of ordinary skill in the art at the time that the invention was made to optimize the conditions to maximize library diversity because the goal of the method is to screen the entire repertoir of antigen binding sites within a particular cell or species.

The rejection is maintained.

7. Claims 1-15, 19, 23, 24 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (1999) US 5,962,255 and Hua et al (1997) Plasmid 38:91-96 for reasons made of record in Paper No. 9.

Applicant argues that Griffiths et al. teach a method of constructing bacterial expression vectors encoding scFv libraries while the presently claimed invention is drawn to a method of generating such expression vectors in yeast.

Applicant argues that Hua et al. teach the optimization of homologous recombination in yeast, and not a method of making scFV libraries in yeast.

Applicant's arguments have been carefully considered and found not to be persuasive.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Additionally, the Hua et al. reference teaches that:

"*Functional analysis of a new gene usually involves many molecular biological technologies, including...gene expression in a heterologous host such as yeast, and two hybrid systems for studying protein-protein interactions. These technologies involve many steps of DNA*

*manipulation and are rather time-consuming. Simplifying the cloning process would increase research efficiency and reduce the cost of investigation.*" (page 91, column 1)

Here the Hua et al. reference provides motivation for one of ordinary skill in the art to apply the method of homologous recombination to large-scale screenings of protein-protein interactions (such as antibody-antigen or scFv-antigen interactions). One of ordinary skill in the art would have been motivated to make the libraries of Griffiths et al. using the method of Hua et al. for the reasons stated by Hua et al. and because, unlike bacteria, yeast can glycosylate proteins. Glycosylation of proteins had well established advantages over non-glycosylated proteins at the time that the invention was made. Although the method of Griffiths et al. involved surface display of phages, it would have been obvious to one of ordinary skill in the art at the time that the invention was made to use the yeast two-hybrid system to make the same scFv libraries for the reasons provided by Hua et al.

The rejection is maintained.

**New Grounds of Rejection Necessitated by Applicant's Amendment**

**New Grounds of Rejection – 35 U.S.C. 112, first paragraph**

8. Claims 44-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention (NEW MATTER).

In accordance with MPEP 714.02, applicant should specifically point out support for any amendment made to the disclosure. Applicant has not indicated where support for the newly added claims can be found in the specification and claims as originally filed. Applicant may overcome this rejection by indicating where support for the newly added claims can be found in the specification and claims as originally filed.

**New Grounds of Rejection – 35 U.S.C. 112, second paragraph**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claim 44-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. In claim 44 the relationships between the overlapping PCR, first PCR, and second PCR are not clear. Both the first and second PCR fragments have linker sequences and it appears that the final product has only one linker between the PCR fragments. It appears that the first and second PCR fragments chare the same linker sequence and that the duplication is somehow removed in the process of overlapping PCR. It is not clear, however, what method steps are used involved in "overlapping PCR."

B. It is not clear what the metes and bounds of "overlapping PCR" are in claim 44 and no definition is provided in the specification for "overlapping PCR."

C. In claims 45 and 46, nucleotide sequences are recited as encoding genes. For example, in claim 45; "the first nucleotide sequence and the second nucleotide sequence respectively encode a heavy chain variable region and a light chain variable region of immunoglobulins genes..." The term "encoding" is used in the art to designate sequences that are translated into protein. As written, the claims seem to indicate that nucleic acid sequence "encode" parts of genes (DNA sequences) rather than proteins. This is confusing and can be clarified by changing the language to indicate that nucleic acid sequences "encode" (for example) light chain and heavy chain variable fragments of immunoglobulins.

**New Grounds for Rejection – 35 U.S.C. 103**

10. Claims 44-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeffler et al. (1999) WO 99/28502, Hua et al (1997) Plasmid 38:91-96, and Filupa et al. (1998) WO 98/49198.

The teachings of the three references as well as motivation for combination and expectation for success with respect to claims 1-15, 19, 23, 24 are described in the preceding rejection of these claims under the heading "Maintained Rejections-35 U.S.C. 103(a)."

With respect to the use of overlapping PCR to generate insert nucleotide sequences, the use of human, non-human primate, and rat immunoglobulins genes, and transcription factors either separate or fused to scFv molecules of the presently claimed method, these would all have been matter of design choice well within the abilities of one of ordinary skill in the art to determine. PCR as a means of generating DNA fragments for cloning was routinely used at the time that the invention was made. The use of human heavy and light chain variable regions, for example, is taught in Hoeffler et al. on page 7. The use of transcriptional activators with DNA-binding domains and trans-activator domains separated or together (including GAL4 and ADR1) are taught on page 12 of Hoeffler et al. Fusions between variable domains and DNA-binding domains or trans-activator domains are taught on page 16 of Hoeffler et al.

Accordingly, present claims 44-50 are unpatentable over Hoeffler et al., Hua et al., and Filupa et al.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas Prasthofer** at telephone number **(703) 308-4548**. The examiner can normally be reached on Monday, Tuesday, Friday, and Saturday 8:00-6:30.

13. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

14. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist at (703) 308-1235.

Thomas Prasthofer, Ph.D.

September 19, 2001

DR. JYOTHSNA VENKAT PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600